The PharmGKB experience: an online knowledge base on pharmacogenomics

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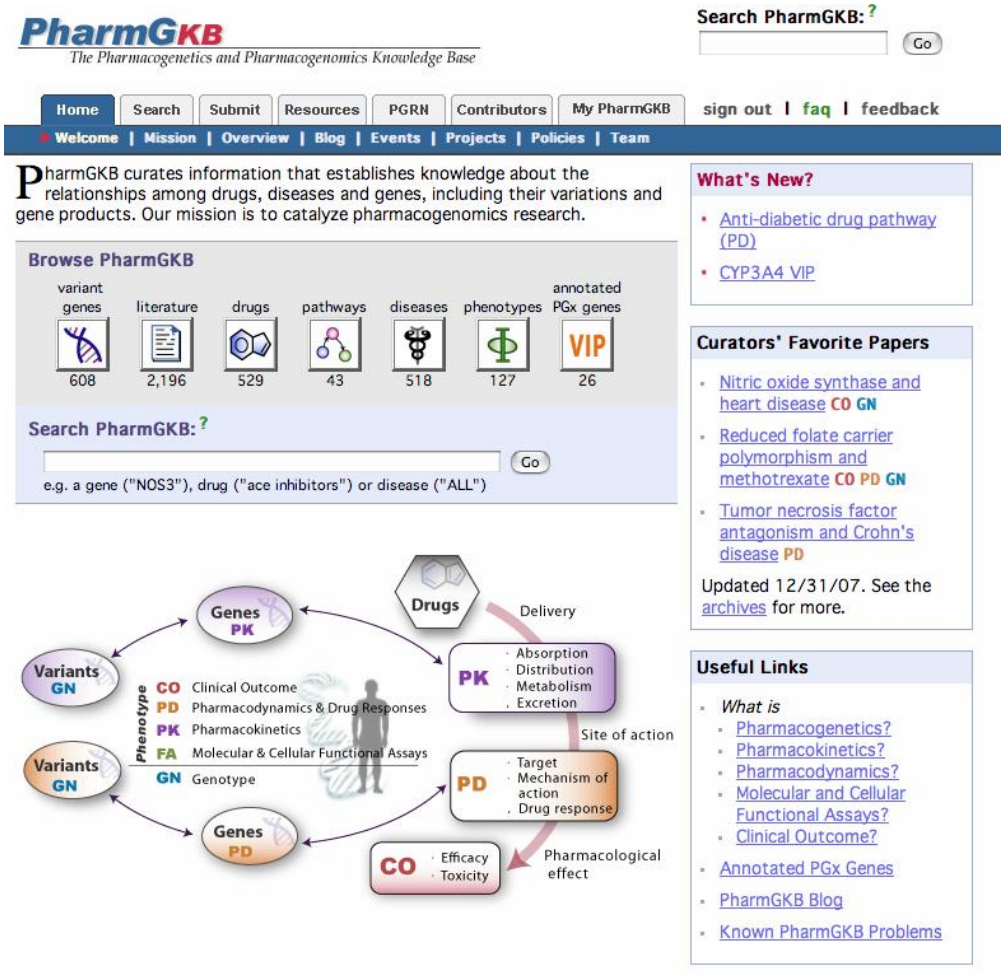
PharmGKB (http://www.pharmgkb.org)

PharmGKB homepage



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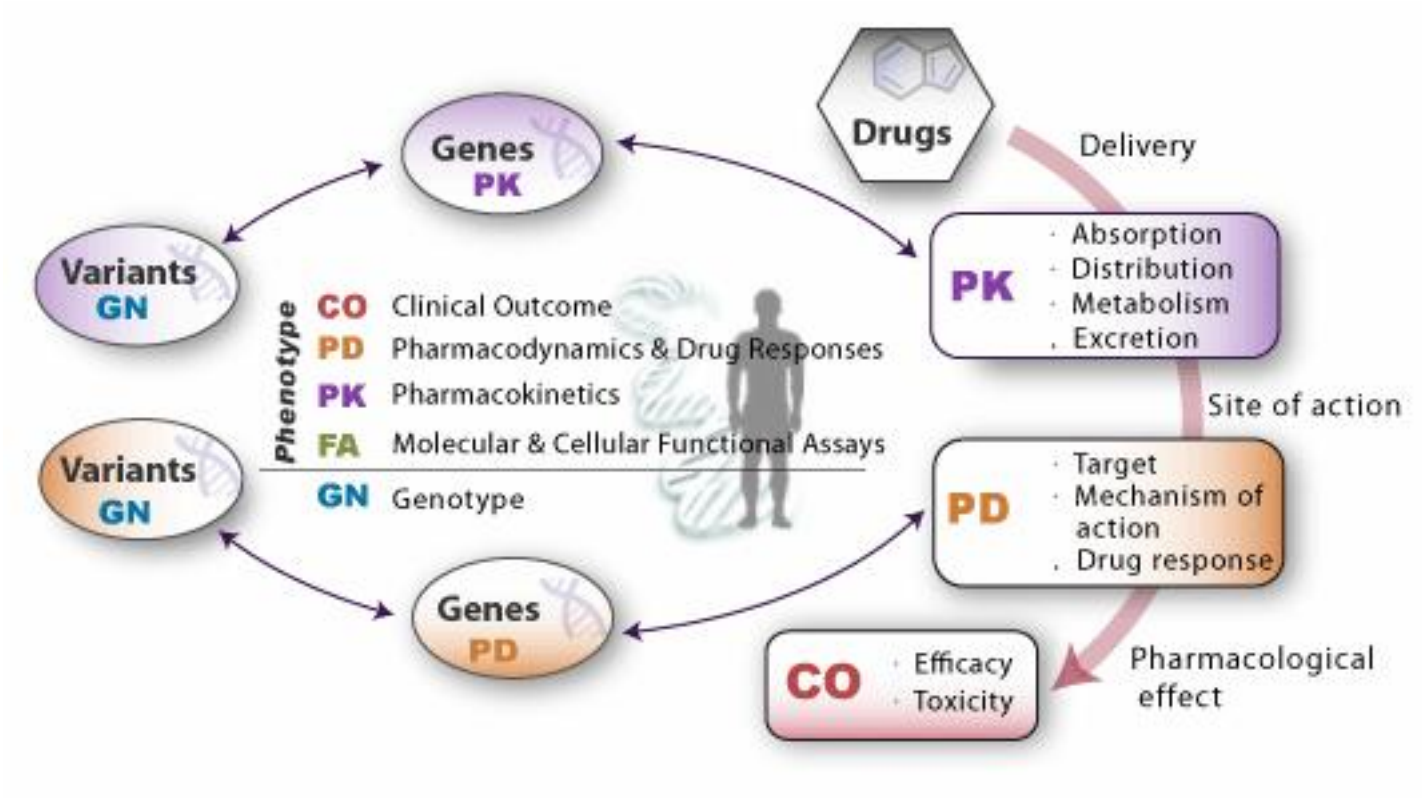
Category of evidence flow chart



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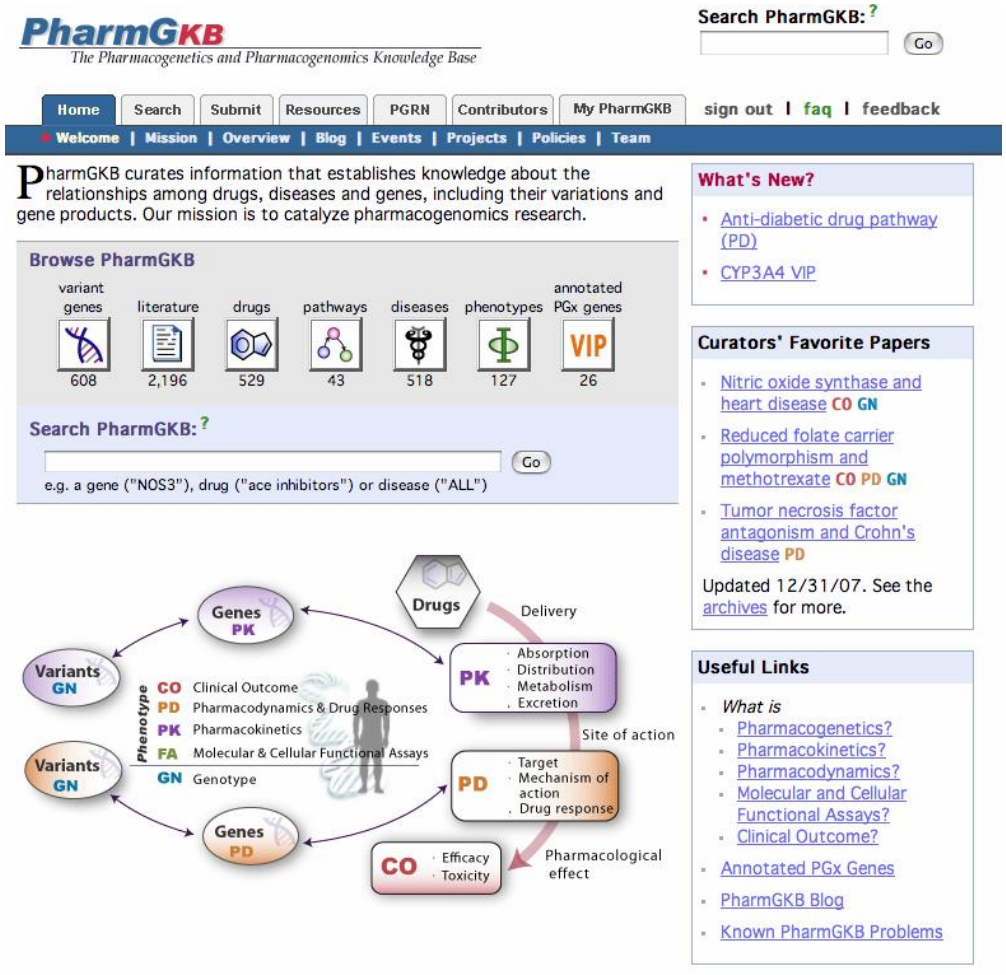
PharmGKB homepage



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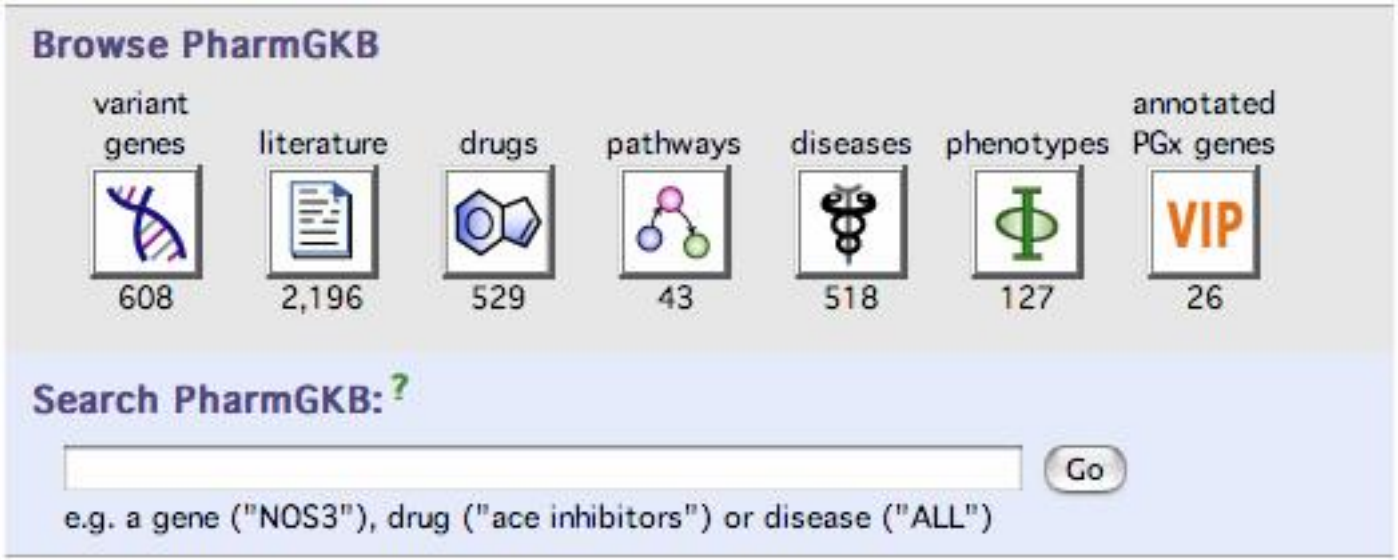
PharmGKB icons



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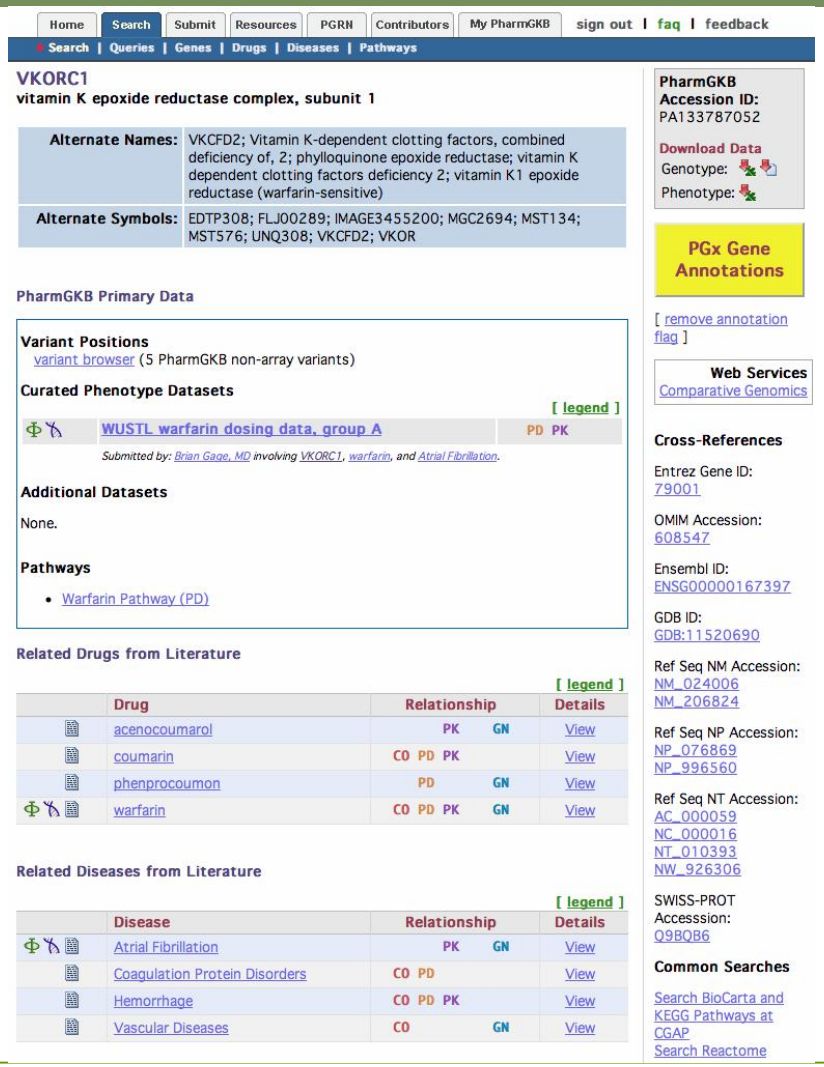
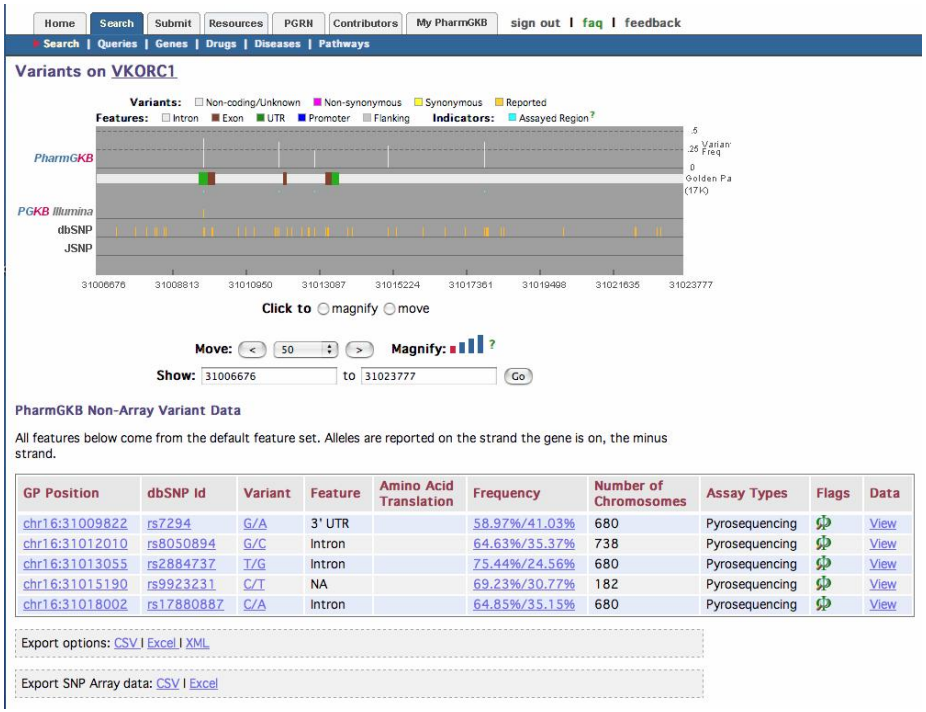
PharmGKB gene page





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Literature annotation

PharmGKB
The Pharmacogenetics and Pharmacogenomics Knowledge Base

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Search | Queries | Genes | Drugs | Diseases | Pathways

Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose

by Rieder Mark J, Reiner Alexander P, Gage Brian F, Nickerson Deborah A, Eby Charles S, McLeod Howard L, Blough David K, Thummel Kenneth E, Veenstra David L, Rettie Allan E in *N Engl J Med* (2005).

Overview | Related Data

Relationships

Gene/Drug/Disease	Relationship
VKORC1, warfarin, Atrial Fibrillation	Discussed

Categories of Pharmacogenetic Knowledge ?

PK Pharmacokinetics
GN Genotype

Abstract

BACKGROUND: The management of warfarin therapy is complicated by a wide variation among patients in drug response. Variants in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) may affect the response to warfarin. METHODS: We conducted a retrospective study of European-American patients receiving long-term warfarin maintenance therapy. Multiple linear-regression analysis was used to determine the effect of VKORC1 haplotypes on the warfarin dose. We determined VKORC1 haplotype frequencies in African-American, European-American, and Asian-American populations and VKORC1 messenger RNA (mRNA) expression in human liver samples. RESULTS: We identified 10 common noncoding VKORC1 single-nucleotide polymorphisms and inferred five major haplotypes. We identified a low-dose haplotype group (A) and a high-dose haplotype group (B). The mean (+/-SE) maintenance dose of warfarin differed significantly among the three haplotype group combinations, at 2.7+/-0.2 mg per day for A/A, 4.9+/-0.2 mg per day for A/B, and 6.2+/-0.3 mg per day for B/B (P<0.001). VKORC1 haplotype groups A and B explained approximately 25 percent of the variance in dose. Asian Americans had a higher proportion of group A haplotypes and African Americans a higher proportion of group B haplotypes. VKORC1 mRNA levels varied according to the haplotype combination. CONCLUSIONS: VKORC1 haplotypes can be used to stratify patients into low-, intermediate-, and high-dose warfarin groups and may explain differences in dose requirements among patients of different ancestries. The molecular mechanism of this warfarin dose response appears to be regulated at the transcriptional level.

Keywords

NEJM, VKORC1, anticoagulation, dosage, haplotypes, mRNA expression, promoter, vitamin K epoxidase, wafarin dose

PharmGKB Accession ID: PA135682081

Download Data
Genotype:
Phenotype:

Cross-References

PubMed ID: 15930419

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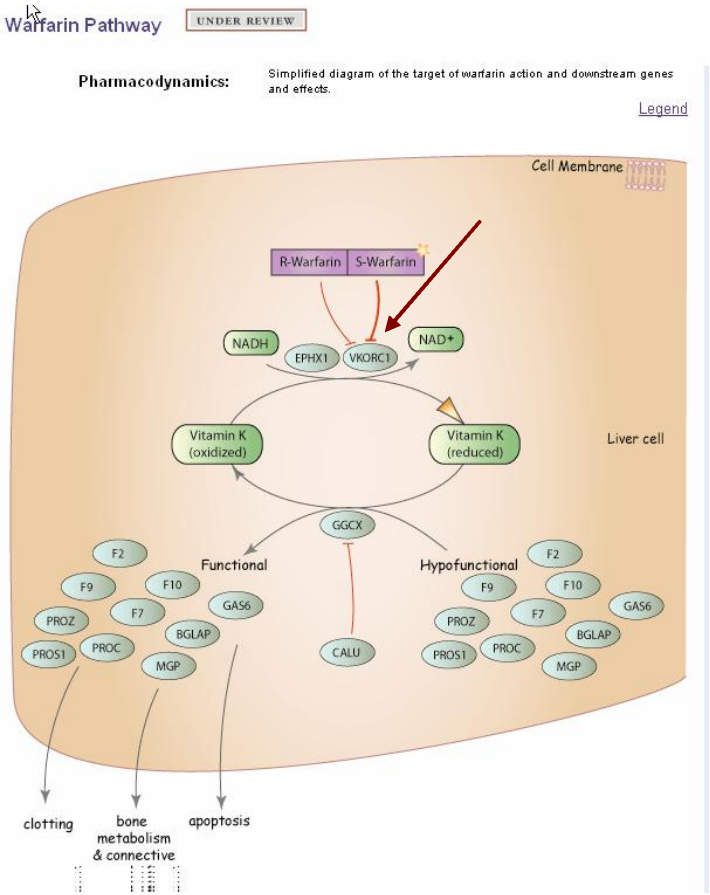
Pathway



A pathway legend is included below the pathway

A link to download the evidence spreadsheet is provided to the right

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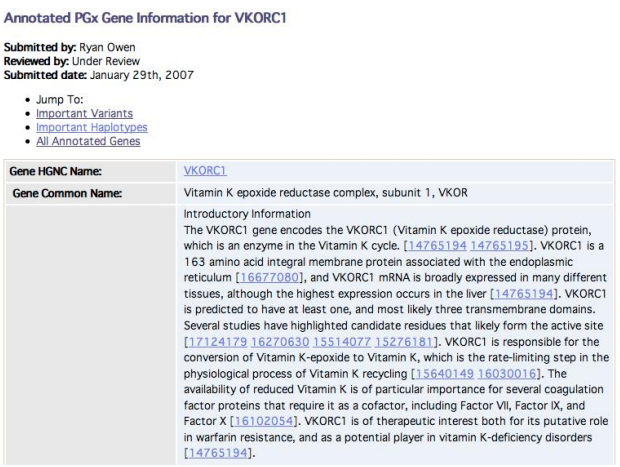
Very Important Pharmacogene (VIP)



Annotated PGx Gene Information for VKORC1

Submitted by: Ryan Owen
Reviewed by: Under Review
Submitted date: January 29th, 2007

- Jump To:
- Important Variants
- Important Haplotypes
- All Annotated Genes

Gene HGNC Name:	VKORC1
Gene Common Name:	Vitamin K epoxide reductase complex, subunit 1, VKOR
	Introductory Information The VKORC1 gene encodes the VKORC1 (Vitamin K epoxide reductase) protein, which is an enzyme in the Vitamin K cycle. [14765194 14765195]. VKORC1 is a 163 amino acid integral membrane protein associated with the endoplasmic reticulum [16677080], and VKORC1 mRNA is broadly expressed in many different tissues, although the highest expression occurs in the liver [14765194]. VKORC1 is predicted to have at least one, and most likely three transmembrane domains. Several studies have highlighted candidate residues that likely form the active site [17124179 16270630 15514077 15276181]. VKORC1 is responsible for the conversion of Vitamin K-epoxide to Vitamin K, which is the rate-limiting step in the physiological process of Vitamin K recycling [15640149 16030016]. The availability of reduced Vitamin K is of particular importance for several coagulation factor proteins that require it as a cofactor, including Factor VII, Factor IX, and Factor X [16102054]. VKORC1 is of therapeutic interest both for its putative role in warfarin resistance, and as a potential player in vitamin K-deficiency disorders [14765194].

Key PubMed IDs:	14765194 14765195 16677080 15640149 16030016 16102054 17110455 17124101 15930419 16270629 16869821 17161452 16960144 16888441 16722840 11127854 14676821 17111199 17048007 17015052 16815313 17042764 15947090 15597574 15865594 15938684 16983400 15358623 9684798
Drugs/Substrates:	Warfarin, Coumarin, Acenocoumarol
Phenotypes/Diseases:	Atrial Fibrillation, Coagulation Protein Disorders, Hemorrhage, Vascular Diseases
Important Variants:	G3673A, C6484T, G9041A
Important Haplotypes:	VKORC1*1, VKORC1*2, VKOC1*3, VKORC1*4

VIP genes all have at least one variant and/or haplotype page

VIP may have endogenous roles in addition to pharmacological roles

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Features of a VIP variant page

G3673A, or -1639 G>A as it is commonly called in the literature, is a polymorphism in the promoter region of VKORC1 that is believed to be the causative SNP for the low dose phenotype. Luciferase assays show that the activity of the G allele was increased by 44% over the activity of the A allele [15888487]. Additionally, analysis of VKORC1 mRNA isolated from human liver samples showed that carriers of the A allele at position 3673 had reduced amounts of VKORC1 mRNA [15930419]. Both of these studies support the contention that the G3673A SNP likely disrupts the binding of a transcription factor in the promoter region of VKORC1 which in turn leads to a lower amount of VKORC1 mRNA transcript, and presumably fewer functional copies of the mature VKORC1 protein.

Population	N	Allele Frequency of "A"	PMID
Japanese	93	93%	17049586
Swedish	181	39%	17048007
Japanese (anticoagulated)	260	89%	16890578
Japanese (healthy)	228	94%	16890578
Spanish (anticoagulated)	105	52%	16611310
Florida VA hospital	356	34%	16580898
German	200	42%	16270629
English	297	47%	15947090
Caucasian	92	37%	15888487
Chinese	95	91%	15888487
Chinese on warfarin	104	88%	15888487
Swedish	201	39%	15883587
French	263	42%	15790782
Japanese	828	91%	16432637

Genomic Variant & GenBank ID:	G3673A (-1639 G>A) on AY587020
mRNA Variant & GenBank ID:	N/A
Protein Variant & GenBank ID:	N/A
dbSNP rs#:	rs9923231 sometimes also appears in the literature as rs17878363
GoldenPath Position:	chr16:31015190-31015190 (hg17)

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New PharmGKB initiatives

- PharmGKB and the formation of the IWPC

- Significant variants project

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Warfarin story

- Used to thin blood, prevent clots/strokes/heart attacks
- Very difficult to dose - can't predict based on size of patient
- Overdose and underdose are both dangerous
  - Narrow therapeutic range

Factors in warfarin response

- Gender
- Ethnicity
- Smoking status
- Height/weight
- Comorbidities
- Other medications
- VKORC1 genotype
- CYP2C9 genotype

PharmGKB and the IWPC

- International collaboration of warfarin pharmacogenetics investigators to share data on PharmGKB
- Why the need?
  - Numerous warfarin datasets with a low N
  - External validity of dosing algorithms?
  - Associations consistent in various groups?

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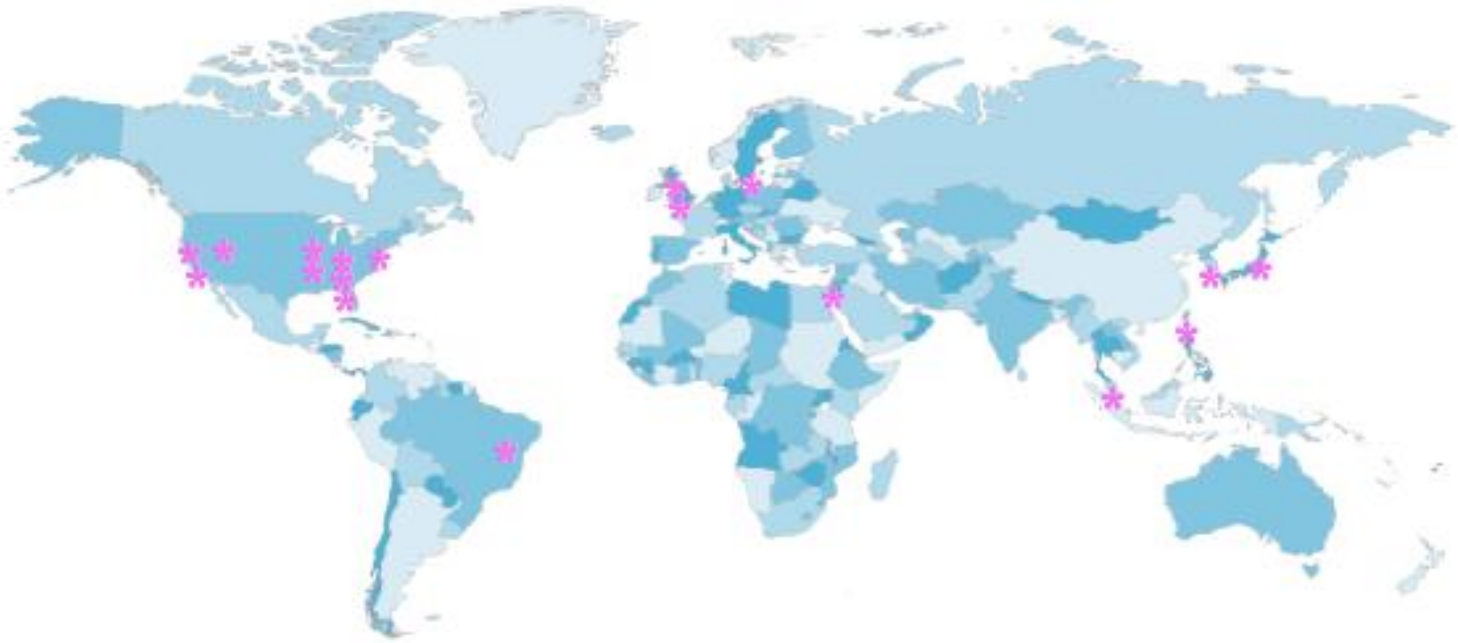
IWPC membership

- Spearheaded by Michael Caldwell (Marshfield Clinic) and Julie Johnson (University of Florida)
- Members must agree to a memorandum of understanding (MOU)
  - No publications of independent analysis until publication of the alpha paper
  - Agree to share data with the rest of the network, and eventually the general public
- A minimal dataset was defined for each group
- Submission of all other available data encouraged

IWPC members



IWPC centers are located in 9 different countries across 4 continents!

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Goals of the IWPC

- To define a dosing algorithm for potential use in NHLBI genotype-guided warfarin clinical trial (expected summer 2008)
- Single equation or race/ethnicity specific
- Determine consistency of associations across ancestral populations
- Define role of various interacting drugs
- Alpha paper is expected later in 2008

PharmGKB variants project

- "Significant" SNPs represent a small proportion of known SNPs
- User feedback
- What makes a SNP significant?
  - Functional change in vitro
  - Haplotype tagging SNP
  - Associated with diseases
  - Clinical differences

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Significant variant information

Type of curation	Automatic	Manual
How obtained?	Pulling from other databases	Reading the literature
Confidence rating	1 star	2 or 3 stars
Best feature	Faster	In depth
Focus on	Available data	Future VIPs

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Sample Information

PharmGKB Non-Array Variant Data

★ Non-curated
★★ Curated
★★★ In-depth

All features below come from the default feature set. Alleles are reported on the strand the gene is on, the plus strand.

GP Position	dbSNP Id	Variant	Feature	Amino Acid Translation	Frequency	Number of Chromosomes	Assay Types	Flags Annotation	Data
chr15:72828394	rs17861148	T/G	Intron		90.73%/9.27%	356	TaqMan		View
chr15:72828404	rs12720461	C/T	Intron		99.72%/0.28%	358	TaqMan		View
chr15:72828970	rs762551				.			★★	
chr15:72829195		C	Exon	Phe	100%	356	TaqMan		View
chr15:72829262	rs3743482	G	Exon	Glu	100%	356	TaqMan		View
chr15:72829438	rs17861154	C	Exon	Gly	100%	356	TaqMan		View
chr15:72829545		G/A	Exon	**Arg/His**	99.43%/0.57%	350	TaqMan		View
chr15:72829634		G	Exon	Glu	100%	354	TaqMan	★	View

- Mapping information to UCSC Golden path, and dbSNP

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chr15:72828404	rs12720461	C/T	Intron		99.72%/0.28%	358	TaqMan		View
chr15:72828970	rs762551				.			★★	
chr15:72829195		C	Exon	Phe	100%	356	TaqMan		View
chr15:72829262	rs3743482	G	Exon	Glu	100%	356	TaqMan		View
chr15:72829438	rs17861154	C	Exon	Gly	100%	356	TaqMan		View
chr15:72829545		G/A	Exon	**Arg/His**	99.43%/0.57%	350	TaqMan		View
chr15:72829634		G	Exon	Glu	100%	354	TaqMan	★	View

- Clicking on the stars would bring up a pop up window with more information, including a description of why the variant is significant

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Conclusions

- PharmGKB is an online knowledge base of pharmacogenetics/pharmacogenomics
  - Genes, drugs, and diseases
  - Pathways and VIPs
- Emerging role: host of drug consortia
  - Tamoxifen
- Responsive to user feedback
  - Significant variants

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  - Feng Liu
  - Ryan Whaley
  - Mark Woon

TC Troung
Tina Zhou

IWPC members

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Email questions to me or to feedback@pharmgkb.org